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**Case Report**

# Acute Recurrent Pancreatitis in a Child With INS-Related Monogenic Diabetes and a Heterozygous Pathogenic CFTR Mutation

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## Abstract

Given the close anatomical and physiological links between the exocrine and endocrine pancreas, diseases of 1 compartment often affect the other through mechanisms that remain poorly understood. Pancreatitis has been associated with both type 1 and type 2 diabetes, but its association with monogenic diabetes is unknown. Patients heterozygous for pathogenic CFTR variants are cystic fibrosis carriers and have been reported to have an increased risk of acute pancreatitis. We describe a 12-year-old patient with monogenic neonatal diabetes due to a pathogenic heterozygous paternally inherited mutation of the insulin gene (INS), c.94 G > A (p.Gly32Ser), who experienced 3 recurrent episodes of acute pancreatitis over 7 months in conjunction with poor glycemic control, despite extensive efforts to improve glycemic control in the past 4 years. Intriguingly, the maternal side of the family has an extensive history of adult-onset pancreatitis consistent with autosomal dominant inheritance and the proband is heterozygous for a maternally inherited, CFTR variant c.3909C > G (p.Asn1303Lys). Paternally inherited monogenic neonatal diabetes may have promoted earlier age-of-onset of pancreatitis in this pediatric patient compared to maternal relatives with adult-onset acute pancreatitis. Further study is needed to clarify how separate pathophysiologies associated with INS and CFTR mutations influence interactions between the endocrine and exocrine pancreas.

**Key Words:** pediatric, pancreatitis, neonatal monogenic diabetes, CFTR, INS

Acute recurrent pancreatitis (ARP) is commonly associated with environmental factors including alcohol consumption and smoking in adults. Although it occurs less commonly in children, childhood ARP seems to have a striking difference in its etiology with genetic mutations or pancreatic anatomic anomalies being the risk factors [1]. Carriers heterozygous for cystic fibrosis causing CFTR mutations do have an increased risk of pancreatic diseases, including diabetes (Type 1 or secondary), acute pancreatitis, chronic pancreatitis, and pancreatic steatorrhea, but have a lower risk of the same conditions than patients with cystic fibrosis [2].

To our knowledge, ARP has not been previously reported in patients with insulin gene (*INS*)-related monogenic diabetes. However, several other causes of congenital diabetes are known to increase the risk of exocrine pancreatic dysfunction, and recent studies have shown an association between decreased pancreas volume and diabetes in both type 1 diabetes (T1D) and type 2 diabetes (T2D) patients [3–5]. The pancreas is approximately 85% exocrine pancreas and less than 2% endocrine pancreas by mass [6]. This marked decrease in pancreatic volume despite the low proportion of endocrine tissue in the organ suggests that diabetes may also impact the exocrine pancreas. About 23% of patients with acute pancreatitis (AP) later develop diabetes, further supporting that pancreatitis and diabetes risk are associated [7].

Here we report a case of a child with paternally inherited *INS*-related monogenic diabetes who developed ARP and was found to be heterozygous for a maternally inherited pathogenic variant in *CFTR*. While the child's *CFTR* variant has not been previously described to cause pancreatic issues in the heterozygous state, ARP is uncommon in children, and her maternal relatives carrying the same allele all experienced a later age-of-onset for the same condition.

## Materials and Methods

As part of clinical care following episodes of ARP, our patient's DNA was submitted for hereditary sequencing pancreatitis panel (Mayo Clinic Department of Laboratory Medicine and Pathology) that included Sanger sequencing of

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the PRSS1 gene; next-generation sequencing of the CFTR, CTRC, and SPINK1 genes; and multiplex ligation-dependent probe amplification of the CFTR gene. A heterozygous pathogenic CFTR variant c.3909C > G (p.Asn1303Lys) and the benign polymorphic CFTR intron 9 poly T alleles 7T/9T were the only variants identified. The patient did not have biallelic pathogenic CFTR mutations. A well-known pathogenic *INS* variant c.94 G > A (p.Gly32Ser) was previously identified as the cause of permanent neonatal diabetes in this patient, similar to several other members of her family, including her father, as described previously [8, 9].

To test for the CFTR variant of interest in close relatives with and without a history of pancreatitis, genomic DNA was extracted from whole saliva sample using the Oragene™ DNA sample collection kit OG-600 (DNA Genotek Inc, Canada) according to the manufacturer's instruction. The coding region and exon-intron boundaries of the CFTR gene were PCR amplified using exon21 primer sequences 5′ ATG TTC ACA AGG GAC TCC AAA 3′ and 3′ CAG CCT TAC CTC ATC TGC AAC 5′. PCR products were purified using QIAquick PCR purification Kit (Qiagen, Valencia, CA, USA). Sanger sequencing was performed with 3730XL DNA analyzer using the BigDye technology (Applied Biosystems, Foster City, CA, USA).

This family consented to participate in the University of Chicago Monogenic Diabetes Registry and related studies, all of which have been approved by the University of Chicago Institutional Review Board.

## Results

The 12-year-old patient was diagnosed with neonatal diabetes mellitus (NDM) at 4 months old due to her significant family history of NDM and a pathogenic, heterozygous, and paternally inherited mutation of INS, c.94G > A (p.Gly32Ser) [8]. The p.Gly32Ser variant is a well-characterized cause of permanent NDM that was identified for the first time in her family [8]. She recently experienced 3 recurrent episodes of acute pancreatitis over 7 months in conjunction with poor glycemic control. During each episode of acute pancreatitis, she experienced abdominal pain and emesis for 1 to 2 days, was hospitalized for 3 to 4 days for pain control and intravenous fluid resuscitation, and recovered in 7 to 10 days. There was no prodrome, viral infection, or major diet change or any triggers identified that may have caused her pancreatitis; however, of note, she was midpubertal during this time.

Lipase levels were over 2000 U/L (ref 11-65 U/L) on first ARP episode and more than or close to 1000 U/L on repeat episodes 3 months and 7 months later, despite some effort at dietary modification. Triglyceride levels were not elevated. Magnetic resonance imaging examinations revealed edematous pancreatic head without biliary or pancreatic ductal dilatation or cholelithiasis, and magnetic resonance cholangiopancreatography at the time of the third episode confirmed normal pancreas anatomy without divisum or pancreatic duct irregularities. Calcium levels were within normal limits (N: 8.4-10.2 mg/dL) throughout all 3 episodes (University of Chicago, Chicago, IL), suggesting that hyperparathyroidism and hypercalcemia were not the cause of these episodes [10]. Stool elastase was >500 mcg/g (N: >200 mcg/g) during the third episode, indicating no evidence of pancreatic insufficiency (Quest Diagnostics, San Juan Capistrano, CA). Immunoglobin (Ig)G1, IgG2, IgG3, and IgG4 levels were also within normal limits during the third episode (Mayo Clinic, Rochester, MN), suggesting that this patient did not have autoimmune pancreatitis [11, 12]. Testing for endomysial antibodies (Mayo Clinic, Rochester, MN), deaminated gliadin IgG antibodies, and tissue transglutaminase IgA antibodies were negative with normal IgA levels (University of Chicago, Chicago, IL) during testing following the third episode. Blood sugars were acutely elevated with minimal ketosis but without acidosis (pH > 7.3) on all occasions. She began treatment with an insulin pump at age 4 following an increase in her hemoglobin H1c (HbA1c), but glycemic control remained chronically suboptimal (HbA1c 10-14% over 4 years prior to and including the ARP episodes), likely due to some combination of puberty-related insulin resistance, low mood, and other psychosocial factors leading to difficulties with adherence, despite extensive efforts by her diabetes support team. Interestingly, despite occasional ketosis with illness or pump malfunction, she has never had any episodes of diabetic ketoacidosis. Her only other admission related to hyperglycemia occurred less than 2 months prior to the first ARP episode, when she had been experiencing additional difficulties with her glycemic control due to a concern for possible insulin pump malfunctions that made it difficult to determine her true insulin requirements. During the admission, it became clear that she did require stronger doses of insulin, but she was discharged on a basal/bolus regimen of multiple daily injections due to family mistrust of the insulin pump. A continuous glucose monitoring system (CGMS) was obtained after the first ARP episode but was used only about 50% of the time. A replacement of her traditional pump was placed after her second ARP episode, but insulin dosing was inconsistent and they did not follow up in clinic until after her third ARP episode. She continued to have poor diabetes control about 3 months after the last ARP episode, but after switching to a newer pump and using her CGMS more consistently, her HbAa1c improved to 8.6% (6 months after last ARP episode) and further improved to 6.8% when checked 2 months after initiation of the automated control insulin delivery system (8 months after last ARP episode). There has been no recurrence of pancreatitis episodes for more than 2 years following the third episode, which may be explained by combination of improved glycemic control (HbA1c 6.4-7.8%, except for 1 time 12.1% after not having CGMS system for about a month), puberty ending (she grew about 5 cm after the last ARP episode but has since stopped growing), improved consistency of insulin delivery (possibly related to ease of use of newer pump, as well as improved psychosocial well-being).

Following the episodes of ARP, the pathogenic heterozygous CFTR variant c.3909C > G (p.Asn1303Lys) was identified through a hereditary pancreatitis panel ordered as part of her clinical care, and this was considered as a possible genetic cause of increased pancreatitis risk in the proband. Intriguingly, the maternal side of the family had an extensive history of adult-onset pancreatitis consistent with autosomal dominant inheritance. The patient's mother was found to also be heterozygous for the pathogenic CFTR p.Asn1303Lys variant, while her paternal grandmother was wild-type (Fig. 1). The mother and several other women on the maternal side of the family had episodes of pancreatitis at various ages in conjunction with gallstones that resolved after cholecystectomy. A maternal great uncle was also described to have a history of recurrent pancreatitis in conjunction with liver disease, possibly

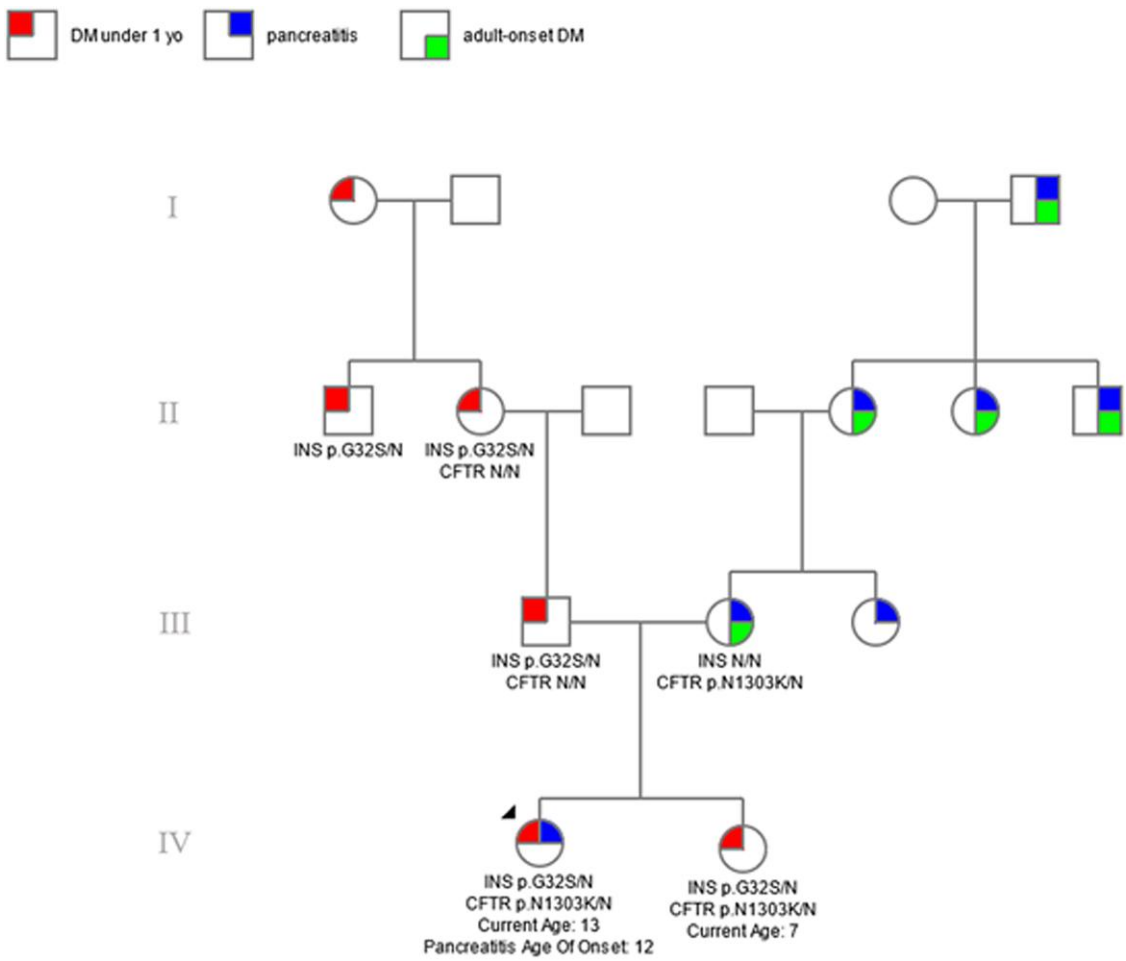


**Figure 1.** Family history of NDM, non-neonatal DM, and pancreatitis. Shaded shape quadrants represent different phenotypes of interest (top left, NDM; top right, pancreatitis; bottom right, non-neonatal DM). Genotypes of each individual for the INS and CFTR variants of interest are listed in relatives of the proband if known and confirmed by Sanger sequencing. A N allele indicates the absence of the INS or CFTR variants of interest on one chromosome. An arrow indicates the proband. (Copyright 2019. Reprinted with permission of Progeny Genetics LLC, Delray Beach, FL, www.progenygenetics.com).

Abbreviations: DM, diabetes mellitus; NDM, neonatal diabetes mellitus; INS, insulin gene.

associated with alcohol consumption, but no other family member had experienced pancreatitis during childhood.

All the proband's maternal relatives with pancreatitis, except for a maternal aunt, were also diagnosed with prediabetes or diabetes later in life. The proband's younger sister, who also has poorly controlled diabetes due to the same pathogenic *INS* variant, also carries the pathogenic CFTR variant but has not yet developed any symptoms of pancreatitis at her prepubertal age of 9 years (Fig. 1).

## Discussion

We report the occurrence of acute recurrent pancreatitis in a patient with a rare CFTR variant likely to predispose to pancreatitis, where the poorly controlled neonatal diabetes due to severe insulin deficiency from her known causal INS mutation may have caused the pancreatitis to occur at an earlier age than CFTR mutation carriers without diabetes. An increased genetic risk of pancreatitis due to the CFTR variant is bolstered by an extensive maternal family history of adult-onset pancreatitis consistent with autosomal dominant inheritance, where it is worth noting that all episodes occurred at much older ages. The extent to which gallstones and/or alcohol or other factors observed in our patient's maternal relatives contributed to their pancreatitis is unclear; however, mouse models and other genetic etiologies of pancreatitis have been described to have predisposing factors leading to pancreatitis episodes. Of note, our patient underwent an extensive evaluation that ruled out any biliary pathology or other causes such as elevated triglyceride levels, which is a common complicating factor in diabetes-associated pancreatitis.

This case thus supports a link between endocrine pancreas dysfunction (diabetes) and exocrine pancreas dysfunction (pancreatitis) as described in Fig. 2. T1D and T2D are associated with decreased pancreas volume, and T2D is associated with increased pancreatic fat content even though only <2% of the pancreas is endocrine tissue and 85% is exocrine tissue by mass [3–6].

Although the exact pathophysiology that may lead T1D patients to develop exocrine pancreas insufficiency is currently unknown, some possibilities include pancreatic inflammation, fibrosis, and steatosis and the reduced impact of insulin [13] or loss of other trophic factors. Autoantibodies to the exocrine pancreas were present at rates up to 39% in T1D patients with decreasing prevalence associated with increased duration

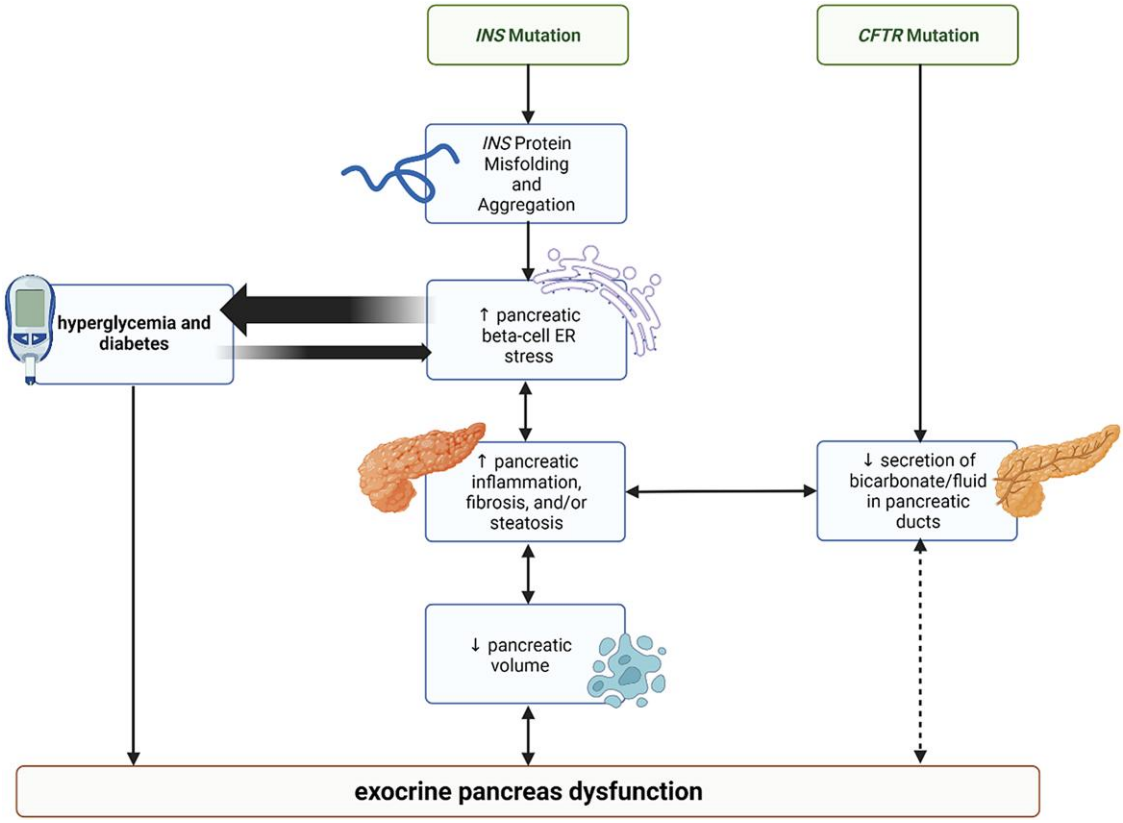


**Figure 2.** Proposed pathophysiological explanation of exocrine pancreas dysfunction in the proband. Created with BioRender.com.

of disease and up to 0.9% in T2D patients but were not detected in patients with alcoholic pancreatitis and controls [14].

Our patient does not have an autoimmune disease like T1D patients, but there may still be a similar insulin deficiency and local breakdown and loss of beta-cells due to her INS-related diabetes that could lead to similar exocrine pancreas phenotypes as seen in T1D patients. A transgenic mouse model overexpressing human islet amyloid polypeptide, a protein involved in T2D pathophysiology that may also play a role in T1D pathophysiology, suggested that islet amyloid polypeptide aggregation led to endoplasmic reticulum (ER) stress and increased beta-cell apoptosis, which led to decreased beta-cell mass and diabetes [15, 16].

The mutant protein encoded by this patient's *INS* variant, p.G32S, is retained in the ER where it misfolds, aggregates, and induces ER stress [17]. The p.G32S variant interferes with disulfide bridge formation at adjacent amino acids and therefore impacts the overall structure and of the protein, leading to its misfolding [8, 18, 19]. A recent mouse model further demonstrated the pathogenicity of the p.G32S proinsulin variant in heterozygous mice who exhibit increased pancreatic beta-cell ER stress, a slight reduction in beta-cell mass, and reduced glucose-stimulated insulin secretion with older age [20]. Ongoing research supports the role of ER stress in the etiology of *INS*-related diabetes. Pharmacologic agents or genetic knockouts that block the ER stress response delay *INS*-related diabetes in the Akita mouse model (who carry the C96Y pathogenic *INS* variant) [21, 22].

However, the exact mechanistic interactions between 1 pathogenic variant (INS) expressed in the pancreatic beta cell and another (CFTR) expressed in the pancreatic duct epithelium remain unknown. Ferret CFTR-knockout models previously demonstrated that dysfunction of 1 gene, CFTR, could lead to dysfunction in both the exocrine pancreas (destruction of the acini and ductules and pancreatic inflammation) and the endocrine pancreas (poor glycemic control and glucose intolerance) [23, 24]. Conversely, a recent study reported that obese *db/db* mice, which develop a model of type 2 diabetes, have increased susceptibility to acute pancreatitis associated with NLRP3 inflammasome activation in the exocrine pancreas. This suggests that loss or dysfunction of pancreatic beta cell mass can predispose the exocrine pancreas to damage and inflammation [25].

The pancreatic beta-cell ER stress response likely to be in our patient may therefore induce increased pancreatic inflammation, fibrosis, and/or steatosis of adjacent acinar cells, leading to decreased overall pancreatic volume and therefore decreased exocrine pancreas function similar to the pathophysiology proposed in patients with typical diabetes (Fig. 2) [3–6, 13, 14].

There are limitations to this study. Both monogenic NDM and ARP have a low frequency in the general population, and pancreatitis has never been reported in patients with INS-related diabetes. It is difficult to establish a causal relationship between monogenic NDM and increased risk of earlier pancreatitis onset with such a low sample size, especially when pancreatitis may not have been well characterized in this population. All genetic testing results found with next-generation methods have a small risk of not detecting small insertions or deletions or rare polymorphisms, leading to a false-positive or -negative test result [26].

It was also unclear exactly how much the CFTR p.N1303K variant contributed to our case's pancreatitis risk compared to the INS p.G32S variant. Cystic fibrosis carrier status was

reported to be a risk factor for conditions like diabetes and pancreatitis [2]. Diminished CFTR function is known to cause decreased secretion of bicarbonate and fluid in the pancreatic ducts. The lowered pH and secretions from the pancreas are then believed to cause or contribute to pancreatic exocrine insufficiency and AP [27]. Several cystic fibrosis patients have reported reduced recurrence of AP during treatment with Ivacaftor, a gene-based cystic fibrosis drug, that subsequently increased after discontinuation of Ivacaftor [28, 29]. Although the association between the CFTR c.3909C > G (p.Asn1303Lys) variant and pancreatitis has not yet been firmly established, this variant has been identified in a pancreatitis cohort [30] as well as in the compound or heterozygous state in a handful of cystic fibrosis patients with steatorrhea, diabetes mellitus, and/or pancreatic insufficiency [31–33]. Altogether, prior research suggests that p.N1303K would increase the pancreatitis risk of our patient but to an unknown extent.

Future investigation of pancreatitis in patients with monogenic causes of diabetes may present a unique opportunity to explore the potential relationship between the pathophysiology of the exocrine and endocrine pancreas and may influence clinical care for some patients with diabetes due to an increased risk of pancreatitis. A 9-year-old patient with monogenic diabetes, cystic fibrosis, and pancreatic insufficiency but not cystic fibrosis-related diabetes was recently reported in the literature [34]. Given the results of this case study, patients with monogenic diabetes like that patient may be at higher risk for AP than previously known, especially if they have an additional risk factor for pancreatitis, such as the CFTR variant in our patient. Although the proband's younger sister has not had pancreatitis despite poor glycemic control and the same pathogenic CFTR variant in the heterozygous state, she has not yet undergone puberty and it is possible she will also develop pancreatitis at a similar age to her older sister if she continues to have poor glycemic control.

Future directions for this family include continued clinical follow-up of both the proband and her younger sister for signs of pancreatitis or other exocrine pancreas complications as well as gathering exocrine pancreas health data from all families with INS-related diabetes enrolled in the US Monogenic Diabetes Registry (including this family) and from families with other monogenic forms of NDM or later onset diabetes. Laboratory research could further elucidate the potential mechanistic relationship between the *CFTR* and *INS* mutations.

There are several clinical recommendations to consider due to the findings of this case report. Optimal glycemic control for patients with INS-related diabetes and other forms of NDM may be necessary to lower pancreatitis risk in addition to previously known diabetes-associated complications. Hereditary pancreatitis panel testing and/or pancreatitis risk counseling may be indicated for pediatric NDM patients who also have a family history or medical history of pancreatitis due to the risk of childhood onset.

In conclusion, this is the first reported case of ARP in a patient with INS-related diabetes and the first report of a patient with pathogenic, heterozygous variants in both the INS and CFTR genes. Since INS-related diabetes is a very rare cause of diabetes, pancreatitis-related phenotypes may not have yet been well characterized in this population. Further investigation is needed to establish the prevalence of pancreatitis in NDM patients as well as whether there is a mechanistic relationship between the CFTR and INS variants that resulted in an earlier age-of-onset of pancreatitis in this patient.

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## Conflict of Interest

S.O. is a founder, equity holder, and consultant for OptiKIRA, LLC (Cleveland, OH). R.S., B.K., T.B., R.A., L.P., and S.G. have nothing to declare.

## Data Availability

Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in the references.

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